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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#14
6-3-03

Applicants : Philip O. Livingston, et al.

Continued Prosecution Application
of Serial No.:09/534,711 Examiner: C. Yaen

Filed :March 24, 2000 Group Art Unit: 1642

For : FUCOSYL GM1-KLH CONJUGATE VACCINE AGAINST SMALL CELL LUNG CANCER

1185 Avenue of the Americas
New York, New York 10036
April 21, 2003

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Attn: Box CPA

Sir:

PRELIMINARY AMENDMENT

Claims 1,2 5-8 and 11-16 are pending in the present application.

In the Final Office Action dated April 22, 2002, the claims of the application were rejected under 35 U.S.C. §103(a) over the combination of Jennemann, et al. ("Jennemann") and Vangsted et al. ("Vangsted") in view of Kensil et al. ("Kensil"). The Examiner stated that Jennemann teaches the administration of a fucosylated GM1 ganglioside conjugated to KLH, and also that, "[t]he administration of similar antigens with QS-21 was able to induce an immune response in humans in the treatment of melanomas", citing to p. 383 of Jennemann. The Examiner additionally stated, in clarification of his statements in the previous Office Action dated July 19, 2001, that Jennemann does not teach QS-21 or Quill A in connection with Fucosylated GM1. (emphasis supplied by applicants). The Examiner then further stated that Vangsted and Kensil provide the motivation and reasonable expectation of success of using a fucosylated GM1 conjugated to a carrier, and

administered to a subject for preventing or treating small cell lung cancer.

In response to the rejections in the Final Office Action, applicants filed a Response thereto on July 16, 2002 in which the claim rejections were traversed and detailed arguments were provided to further distinguish the claimed invention over the prior art cited by the Examiner. Those arguments are specifically incorporated herein by reference thereto.

Pursuant to the filing by applicants of their Response to the Final Office Action, the Examiner issued an Advisory Action in which he stated the following:

> [a]pplicants' arguments have not overcome the obviousness of the combined references. The arguments presented discuss the non-obviousness of the references because Jennemann does not teach the conjugation of the immunoconjugate with QS-21 or Quill A. However, Jennemann et al. does teach the combination of fucosyl GM-1-KLH in combination with Quillaja saponaria Molina saponin adjuvant (fraction QS-21) (see page 383). Therefore, the combination of the Jennemann et al. reference that teaches the invention and the Vangsted and Kensil reference teach the motivation and expectation of success of using the invention. Therefore the rejection is maintained for the reasons of record. (emphasis supplied by applicants).

Applicants note, first, an apparent contradiction in the statements made by the Examiner. That is, on page 2 of the Final Office Action the Examiner stated, "It appears that the last office action was a little confusing with respect to Jennemann et al. and adjuvants such as Quill A or QS21 - the action meant to have conveyed that Jennemann does not teach QS21 or Quill A in conjunction with Fucoslylated GM1." Notwithstanding the position taken in the Final Office Action, however, the Examiner thereafter stated in the Advisory Action, as noted above, that, "Jennemann et al... teach[es] the combination of fucosyl GM1-KLH in combination with Quillaja saponaria Molina saponin adjuvant (fraction QS21)." Applicants respectfully submit that the arguments as made by the Examiner, i.e., that the subject reference teaches fucosyl GM-1-KLH + QS-21 (Advisory Action), but that the reference does not teach QS-21 "in conjunction with" Fucosylated GM1 (Final Office Action) are contradictory and thus do not support a rejection of the claims.

Notwithstanding the above, however, and with specific reference to the Examiner's above-quoted statement in the Advisory Action, Applicants have closely reviewed the entire Jennemann reference, and particularly that portion of the reference cited to by the Examiner, i.e., on p. 383 with regard to the issue of whether or not Jennemann actually does teach fucosyl GM1-KLH+QS21. Applicants respectfully submit that it appears the Examiner has misconstrued the teaching of the reference, as explained below and thus the reference, when properly interpreted, does not teach or suggest the subject combination, whether taken alone or in combination with any of the other cited references.

The relevant text in the Jennemann reference is found in the

paragraph bridging columns 1-2 on p. 383. The authors state:

> Therefore, in an earlier study with the synthesis of a Gfpt1-KLH conjugate [Gfpt is defined at p.378 of the reference as gangliofucopentaose, $IV^2Fuc\text{-}Gg_4$], the development of an effective anti-Gfpt1 immunogen was attempted which could possibly be used as a vaccine in human therapy. [citation omitted]. A <u>similar immune conjugate</u> using KLH and ganglioside Glac2[$II^3(NeuAc)_2$-LacCer] [citation omitted] in the presence of a Quillaja saponaria Molina saponin adjuvant [fraction QS21] [citation omitted] was more recently applied in clinical phase-I trial for the treatment of human malignant melanoma. [citation omitted]. [emphasis supplied by applicants].

Applicants submit, however, that notwithstanding the Examiner's statement to the contrary, the reference clearly does <u>not</u> teach the combination of fucosyl GM1-KLH + QS21. Rather, the reference discloses the addition of QS21 to a "similar immune conjugate" (see the discussion below pertaining to the use of the term "similar") including the ganglioside Glac2. Therefore, it is respectfully submitted that the Examiner's statement in the Advisory Action that the Jennemann reference teaches fucosyl GM1-KLH +QS21 misconstrues the author's teachings and that the reference does not stand for the proposition relied upon by the Examiner to support his rejection of the claims.

Moreover, as referred to above, the Examiner in the Final Office Action stated that (a) Jennemann teaches the administration of a

fucosylated GM1 ganglioside conjugated to KLH, and also that (b) the administration of similar antigens with QS21 was able to induce an immune response in humans in the treatment of melanomas (citing once again to p. 383 of the Jennemann et al. reference). The Examiner was thus clearly attempting to draw from the above characterization the inference that the administration of such "similar antigens" with QS21 would suggest the use of this adjuvant (QS21) with the fucosylated GM1 ganglioside. Applicants note, however, that as demonstrated below the Examiner's characterization of the disclosure of the reference is not supported by the actual words of the reference and thus the reference does not provide a basis for rendering the claimed subject matter obvious, whether taken alone or in combination with the other cited references.

In the portion of the reference cited to by the Examiner, i.e., p. 383, the authors refer to the application of a "similar immune conjugate" (i.e., using KLH and Glac2 in the presence of QS21), and not to a conjugate incorporating a "similar antigen" as stated by the Examiner in the Final Office Action. Thus, what the authors stated was that the conjugate used to treat melanomas was "similar" to applicants' fucosylated GM1 ganglioside-KLH conjugate, i.e., in that both conjugates were composed of an antigen conjugated to the immunogenic protein KLH. There is no showing of "similarity" however, in the Jennemann reference, between the fucosylated GM1 ganglioside antigen as included in the presently claimed composition and method (and as disclosed for use without QS21 or Quill A in the reference), and the Glac2 ganglioside antigen disclosed in Jennemann as being used with a Quillaja saponaria Molina saponaria adjuvant [fraction QS21]. Thus Jennemann provides no teaching or suggestion concerning the issue of whether a

fucosylated GM1 ganglioside is sufficiently "similar" to a Glac2 ganglioside that the addition of a carbohydrate derived from the bark of a Quillaja saponaria Molina tree (as recited, e.g., in applicants' claim 1) would provide any particularly beneficial results. Thus, there is only the Examiner's unsupported supposition that an adjuvant extracted from the Quillaja saponaria Molina tree would provide useful results with a fucosylated GM1 ganglioside, as well as with a Glac2 ganglioside. Therefore, there is no support for the conclusion which the Examiner draws from the cited reference, i.e., that the reference would suggest to one of ordinary skill in the art the inclusion of a QS21 adjuvant with a conjugate of fucosylated GM1 ganglioside to KLH. The only actual support, therefore, for making such a substitution, i.e., for adding QS21 to a conjugate of fucosylated GM1-KLH, is applicants' disclosure as set forth in the specification of the present application, which teaching can not be relied on in support of an "obviousness" rejection under §103(a). Clearly, therefore, the Jennemann reference does not render obvious the presently claimed invention.

As noted above, the Examiner stated in the Advisory Action that (a) the Jennemann et al. reference teaches the invention, and (b) the Vangsted and Kensil reference(s) teach the motivation and expectation of success of using the invention. In response, applicants submit that they have clearly established above that Jennemann neither teaches nor suggests the presently claimed invention. As to the Vangsted and Kensil references, applicants note the following. Vangsted discloses the use of the ganglioside Fucosyl GM1 as a serum marker for small cell lung cancer. The reference, however, is completely devoid of any teaching or

suggestion: (a) to conjugate the Fucosyl GM1 ganglioside to an immunogenic protein, and/or (b) to include with such a conjugate, as an adjuvant, a carbohydrate derived from the bark of a Quillaja saponaria Molina tree (i.e., QS21). Thus, the combination of Jennemann and Vangsted does not suggest applicants' invention to one of ordinary skill in this art.

The Kensil reference reports on the separation and characterization (with regard to adjuvant activity) of saponins extracted from the Quillaja saponaria Molina tree. While the reference does note, on p. 431, col. 2, that crude preparations of Quillaja saponins have been used to boost response to, e.g., Keyhole Limpet Hemocyanin, the reference contains no suggestion to conjugate such Keyhole Limpet Hemocyanin with a Fucosyl GM1 ganglioside, as recited in applicants' claims. The reference is entirely silent with regard to any adjuvant effect of a Quillaja saponaria Molina adjuvant in a composition containing a ganglioside, much less a fucosyl ganglioside (and in particular a fucosyl ganglioside conjugated to KLH) as specifically recited in, e.g., applicants' claim 1. Again, the only teaching or suggestion to make the indicated combination is that found in applicants' specification, as applicants were the first to discover the unexpected advantages provided by the claimed compositions and methods.

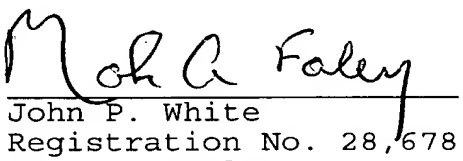
Summary

Therefore, as the cited references do not teach or suggest the invention as presently claimed, whether taken individually or in combination, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-2, 5-8 and 11-16 under 35 U.S.C. §103(a) to permit the subject claims to issue.

If a telephone interview would be of assistance in advancing the prosecution of this application, applicants' undersigned attorneys invite the Examiner to telephone either of them at the number below.

No fee is deemed necessary with the filing of this Preliminary Amendment. However, if any fee is due, authorization is hereby provided to charge the required amount to Deposit Account No. 03-3125.

Respectfully submitted,



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